

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A nucleic acid expression cassette that is predominantly expressed in the mammalian liver, said cassette comprising:

- (a) an hepatic locus control element;
- (b) an hepatic promoter located 3' to the hepatic locus control element;
- (c) a coding sequence located 3' to the hepatic promoter, said coding sequence encoding a polypeptide;
- (d) a polyadenylation signal located 3' to the coding sequence; and
- (e) an intron located 3' to the hepatic promoter and 5' to the polyadenylation signal, wherein elements (a), (b), (c), (d) and (e) are operably linked to express the polypeptide encoded by the coding sequence.

2. The expression cassette of Claim 1, wherein said cassette directs expression of a therapeutic amount of the polypeptide in liver cells for a period of at least 100 days.

3. The expression cassette of Claim 1, wherein said cassette directs expression of a therapeutic amount of the polypeptide in liver cells for a period of at least 300 days.

4. The expression cassette of Claim 1, wherein said cassette directs expression of a therapeutic amount of the polypeptide in liver cells for a period of at least 500 days.

5. The expression cassette of Claim 1, wherein the polypeptide is Factor IX, and wherein the cassette directs expression of the Factor IX in liver cells for a period of at least 200 days.

6. The expression cassette of Claim 1, wherein the polypeptide is Factor IX, and wherein the cassette directs expression of the Factor IX in liver cells for a period of at least 500 days.

7. The expression cassette of Claim 1, wherein the hepatic locus control element hybridizes under stringent conditions to the complement of the hepatic locus control element consisting of the nucleic acid sequence set forth in SEQ ID NO: 4.

8. The expression cassette of Claim 1, wherein the hepatic locus control element consists of the nucleic acid sequence set forth in SEQ ID NO: 4, or the nucleic acid sequence set forth in SEQ ID NO: 9.

9. The expression cassette of Claim 1, wherein the hepatic promoter is a constitutive promoter.

10. The expression cassette of Claim 1, wherein the hepatic promoter is an inducible promoter.

11. The expression cassette of Claim 1, wherein the hepatic promoter comprises at least one hepatic nuclear factor binding site consisting of a nucleic acid sequence selected from the group of nucleic acid sequences set forth in SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14; SEQ ID NO: 15 and SEQ ID NO: 16.

12. The expression cassette of Claim 1, wherein the hepatic promoter hybridizes under stringent conditions to the complement of the hepatic promoter consisting of the nucleic acid sequence set forth in SEQ ID NO: 5.

13. The expression cassette of Claim 1, wherein the hepatic promoter consists of the nucleic acid sequence set forth in SEQ ID NO: 5.

14. The expression cassette of Claim 1, wherein the coding sequence encodes a blood clotting polypeptide.

15. The expression cassette of Claim 1, wherein the coding sequence encodes a Factor IX polypeptide.

16. The expression cassette of Claim 1, wherein the coding sequence encodes a Factor IX polypeptide consisting of the amino acid sequence set forth in SEQ ID NO: 3.

17. The expression cassette of Claim 1, wherein the intron sequence is located 5' to the coding sequence.

18. The expression cassette of Claim 1, wherein the intron sequence is located 3' to the coding sequence.

19. The expression cassette of Claim 1, wherein the intron sequence is located within the coding sequence.

20. The expression cassette of Claim 1, wherein the intron sequence hybridizes under stringent conditions to the complement of an intron sequence located in a gene that encodes the polypeptide encoded by the coding sequence.

21. The expression cassette of Claim 1, wherein the coding sequence encodes a Factor IX polypeptide and the intron is a portion of a Factor IX gene intron.

22. The expression cassette of Claim 1, wherein the intron consists of the nucleic acid sequence set forth in SEQ ID NO: 1.

23. The expression cassette of Claim 1, wherein the polyadenylation signal hybridizes under stringent conditions to the complement of the nucleic acid sequence set forth in SEQ ID NO: 6.

24. The expression cassette of Claim 1, wherein the polyadenylation signal consists of the nucleic acid sequence set forth in SEQ ID NO: 6.

25. A nucleic acid expression cassette that is predominantly expressed in the mammalian liver, said cassette comprising:

- (a) an hepatic locus control element that hybridizes under stringent conditions to the complement of the hepatic locus control element set forth in SEQ ID NO: 4;

- (b) an hepatic promoter located 3' to the hepatic locus control element, said hepatic promoter comprising at least one hepatic nuclear factor binding site comprising a nucleic acid sequence selected from the group of nucleic acid sequences set forth in SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, and SEQ ID NO: 16;

(c) a coding sequence that encodes a polypeptide, said coding sequence located 3' to the hepatic promoter;

(d) an intron located 5' to the coding sequence and 3' to the hepatic promoter; and

(e) a polyadenylation signal located 3' to the coding sequence, wherein elements (a), (b), (c), (d) and (e) are operably linked to express the polypeptide encoded by the coding sequence.

26. The expression cassette of Claim 25, wherein the hepatic locus control element comprises the nucleic acid sequence set forth in SEQ ID NO: 4, the hepatic promoter comprises the nucleic acid sequence set forth in SEQ ID NO: 5, the intron comprises the nucleic acid sequence set forth in SEQ ID NO: 2, and the polyadenylation signal comprises the nucleic acid sequence set forth in SEQ ID NO: 6.

27. A vector comprising a nucleic acid expression cassette that is predominantly expressed in the mammalian liver, said cassette comprising:

(a) an hepatic locus control element;

(b) an hepatic promoter located 3' to the hepatic locus control element;

(c) a coding sequence located 3' to the hepatic promoter, said coding sequence encoding a polypeptide;

(d) a polyadenylation signal located 3' to the coding sequence; and

(e) an intron located 3' to the hepatic promoter and 5' to the polyadenylation signal, wherein elements (a), (b), (c), (d) and (e) are operably linked to express the polypeptide encoded by the coding sequence.

28. The vector of Claim 27, wherein said vector is an episomal vector.

29. The vector of Claim 28, wherein said episomal vector is a plasmid.

30. The vector of Claim 27, wherein said vector is an integrating vector.

31. The vector of Claim 30, wherein said vector is a viral vector.

32. A method of ameliorating the symptoms of a disease, said method comprising the steps of:

(1) introducing into the liver of a mammalian subject a vector comprising a nucleic acid expression cassette, said expression cassette comprising:

- (a) an hepatic locus control element;
- (b) an hepatic promoter located 3' to the hepatic locus control element;
- (c) a coding sequence located 3' to the hepatic promoter, said coding sequence encoding a polypeptide;
- (d) a polyadenylation signal located 3' to the coding sequence;
- (e) an intron located 3' to the hepatic promoter and 5' to the polyadenylation signal, wherein elements (a), (b), (c), (d) and (e) are operably linked to express the polypeptide encoded by the coding sequence; and

(2) expressing a therapeutic amount of said polypeptide in the liver.

33. The method of Claim 32, wherein the polypeptide is a blood clotting factor.

34. The method of Claim 32, wherein a therapeutic amount of the polypeptide is expressed for at least 200 days.

35. The method of Claim 32, wherein a therapeutic amount of the polypeptide is expressed for at least 500 days.